ACUTE CORONARY SYNDROMES

Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST segment elevation acute coronary syndromes: benefit and harm in different age subgroups

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Objective: To investigate whether the beneficial and harmful effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST elevation acute coronary syndromes (NSTE-ACS) depend on age.

Methods: A meta-analysis of six trials of platelet glycoprotein IIb/IIIa receptor blockers in patients with NSTE-ACS (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, GUSTO IV-ACS; n = 31 402) was performed. We applied multivariable logistic regression analyses to evaluate the drug effects on death or non-fatal myocardial infarction at 30 days, and on major bleeding, by age subgroups (<60, 60–69, 70–79, ⩾80 years). We quantified the reduction of death or myocardial infarction as the number needed to treat (NNT), and the increase of major bleeding as the number needed to harm (NNH).

Results: Subgroups had 11 155 (35%), 9727 (31%), 8468 (27%) and 2049 (7%) patients, respectively. The relative benefit of platelet glycoprotein IIb/IIIa receptor blockers did not differ significantly (p = 0.5) between age subgroups (OR (95% CI) for death or myocardial infarction: 0.86 (0.74 to 0.99), 0.90 (0.80 to 1.02), 0.97 (0.86 to 1.10), 0.90 (0.73 to 1.16); overall 0.91 (0.86 to 0.99). ORs for major bleeding were 1.9 (1.3 to 2.8), 1.9 (1.4 to 2.7), 1.6 (1.2 to 2.1) and 2.5 (1.5–4.1). Overall NNT was 105, and overall NNH was 90. The oldest patients had larger absolute increases in major bleeding, but also had the largest absolute reductions of death or myocardial infarction. Patients ⩾80 years had half of the NNT and a third of the NNH of patients <60 years.

Conclusions: In patients with NSTE-ACS, the relative reduction of death or non-fatal myocardial infarction with platelet glycoprotein IIb/IIIa receptor blockers was independent of patient age. Larger absolute outcome reductions were seen in older patients, but with a higher risk of major bleeding. Close monitoring of these patients is warranted.

Platelet glycoprotein IIb/IIIa receptor blockers decrease the risk of death or non-fatal myocardial infarction at 30 days in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) who are not routinely scheduled for early revascularisation.[1–4] Age is an important risk factor for these patients, and if the relative benefits of effective interventions are the same across age groups, doctors should treat older patients even more aggressively than younger patients, as the absolute benefit may be larger.[5] However, in clinical practice, utilisation of platelet glycoprotein IIb/IIIa receptor blockers is lower among older patients.[6]

Older patients may be undertreated because of several reasons; they may be under-represented or excluded from randomised clinical trials, or clinicians may believe that benefits in younger patients may not generalise to the older patients or they may be worried about harmful effects in older patients.[5] Researchers have variously reported that the benefit of platelet glycoprotein IIb/IIIa receptor blockers is greater in younger patients,[7] similar in older and younger patients,[8] or greater in older patients given their higher baseline risk.[5 9] However, across it is difficult to determine how the efficacy of platelet glycoprotein IIb/IIIa receptor blockers varies across age subgroups because most trials are not large enough to provide a reliable answer. Individual acute coronary syndrome (ACS) trials have been inconclusive or even conflicting regarding the presence or absence of relative differences in drug effects across ages.[10–15] Usually, the patient population was split only into two age groups (eg, <65 years, ⩾65 years),[11 13–15] and different primary end points were considered. An evaluation of the drug effects across age groups in a meta-analysis using individual data can better define its relative and absolute efficacies in older versus younger patients.

One more issue is relevant in the interpretation of the effects of platelet glycoprotein IIb/IIIa receptor blockers by age groups. The incorporation of harmful major bleeding rates in the evaluation of effects should be considered to further understand the net drug effectiveness across age strata.[5 9 16]

We investigated whether the relative effects of platelet glycoprotein IIb/IIIa receptor blockers were consistent across age subgroups in patients with NSTE-ACS. Further, we evaluated whether the absolute benefits and harms differed across age subgroups.

METHODS

Trial selection

A meta-analysis of individual patient data was performed, including trials reported since 1990 with the following characteristics: randomisation of patients with NSTE-ACS, comparison of a platelet glycoprotein IIb/IIIa receptor blocker with placebo or control therapy, no recommendation for early (<48 h) coronary revascularisation during study–drug infusion, and enrolment of at least 1000 patients. Six trials met the inclusion criteria (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B and GUSTO IV-ACS)[10–15] with a total

of 31 402 patients. Details of the trial designs are available elsewhere.[3]

Patients' baseline characteristics

An electronic database consisting of data from individual patients in all eligible trials was available.[3] These data were checked for completeness, for internal consistency of patients' records, and for consistency with the published reports. For this analysis, baseline characteristics regarded as important predictors of the outcome for which information was almost complete (ie, <1% missing) were age, sex, diabetes, smoking, previous myocardial infarction, previous heart failure, previous coronary artery bypass surgery (CABG), previous percutaneous coronary intervention (PCI) and ST segment depression. Other important predictors had >20% of missing data: blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n = 7800, 25%), and baseline creatine kinase myocardial band (CK-MB) was missing in 7469 patients (24%) across different trials. Blood pressure, heart rate and CK-MB were used in addition to the other predictors in secondary analyses that yielded largely similar results.

End points

For this analysis, the primary efficacy end point was defined a priori as the composite of death from any cause or non-fatal myocardial infarction at 30 days. Myocardial infarction was a part of the composite outcome of all trials. The myocardial infarction definitions had subtle differences across trials regarding the CK-MB threshold[3] (table 1). However, all trials had prespecified definitions of myocardial infarction.[17 18] Secondary end points were: death, non-fatal myocardial infarction, CABG, PCI, and CABG or PCI. The primary harm end point was major bleeding within 30 days. Individual trial definitions of major bleeding also had subtle differences at most, and trial-specific definitions were retained.[3] We should acknowledge that death or non-fatal myocardial infarction and major bleeding do not have the same utility, and therefore are not comparable events. A few patients with major bleeding died or had a myocardial infarction within 30 days, and not all of the remaining patients had long-term negative outcomes. Determining the relative weights of these events is largely subjective. A recent review identified that the weight of a major bleeding related to a drug in the context of an ACS was 0.87, compared with the weight of death, which was equal to zero.[19]

Efficacy analysis by age

We divided the patient data into four subgroups according to age: <60, 60–69, 70–79 and ≥80 years. The decision to group patients in these intervals was made a priori, and was taken on the basis of decade intervals of common clinical use. The choice of other cut-off points (eg, quartiles) yielded similar results (not shown). Relative differences between platelet glycoprotein IIb/IIIa receptor blockers and placebo/control on the primary end point by age subgroups were assessed, within each trial and across all trials. Logistic regression models were used, and ORs and corresponding 95% CIs were calculated. To evaluate platelet glycoprotein IIb/IIIa receptor blocker effect modification by age in each individual trial and in all trials, interaction tests were used.[20] These tests also evaluated heterogeneity of effects across trials. The effects of platelet glycoprotein IIb/IIIa receptor blockers and the interactions were adjusted for the previously described predictors, for trial, and for potential differences in age-related trends between trials. These effects were combined using random effects calculations.[21] Heterogeneity of interactions across trials was evaluated with the random effects inverse variance model (with trial being the random effect).[22]

Benefit and harm of platelet glycoprotein IIb/IIIa receptor blockers by age subgroups

We performed analyses that incorporated the relationship between the baseline risk (eBR, proportion of patients in the placebo/control group with the primary efficacy end point), the efficacy odds ratio (eOR) and the respective number needed to treat (NNT). The calculation of NNT was performed using eBR and eOR, with the formula:[22]

$$(1eBR(1eOR))/(eBR(1eBR)(1eOR))$$

NNT is the number of patients who need to be treated in order to prevent one additional death or non-fatal myocardial infarction, and is the inverse of the absolute risk reduction. Furthermore, we looked at the relationship among the baseline proportion of the primary harm end point in the placebo/control group (hBR), the harm odds ratio (hOR) and the respective number needed to harm (NNH). The NNH was calculated using hBR and hOR, with the formula:[23]

$$(hBR(hOR1)+1)/(hBR(1hBR)(hOR1))$$

The NNH is the number of patients who need to be treated in order to cause one major bleeding, and is the inverse of the absolute risk increase. The NNT and NNH calculations were performed overall and by age subgroups.

Table 1 Definitions of primary efficacy and harm end points across trials

	PRISM	PRISM-PLUS	PARAGON-A	PURSUIT	PARAGON-B	GUSTO ACS-IV
Primary efficacy end point	Death, MI or refractory ischaemia at 48 h	Death, MI or refractory ischaemia at 7 days	Death of MI at 30 days	Death or MI at 30 days	Death, MI or severe, recurrent ischaemia at 30 days	Death or MI at 30 days
Required level of CK or CK-MB elevation in MI definition	2×ULN	2×ULN; in relation to PCI: 3×ULN	2×ULN	1×ULN; in relation to PCI: 3×ULN; in relation to CABG: 5×ULN	2×ULN; in relation to PCI: 3×ULN; in relation to CABG: 5×ULN	3×ULN
Primary harm end point: major bleeding	Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration ≥50 g/l; or cardiac tamponade	Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration ≥40 g/l; bleeding requiring transfusion ≥2 units blood; or bleeding requiring surgery	Intracranial haemorrhage; bleeding leading to haemodynamic compromise requiring intervention	Intracranial haemorrhage; bleeding leading to haemodynamic compromise requiring intervention	Intracranial haemorrhage; bleeding leading to haemodynamic compromise requiring intervention	Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration ≥50 g/l

CABG, coronary-artery bypass graft; CK, creatine kinase; CK-MB, creatine kinase fraction myocardial band; MI, myocardial infarction; PCI, percutaneous coronary intervention; ULN, upper limit of normal.

Table 2 Patient characteristics by age subgroups.

	<60 years (n = 11 155)		60–69 years (n = 9727)		70–79 years (n = 8468)		⩾80 years (n = 2049)	
	n	%	n	%	n	%	n	%
Sex								
Male	8275	74	6274	65	4841	57	997	49
Diabetes								
Yes	1771	16	2360	24	2269	27	461	23
Smoking								
Never	3931	35	3439	36	3269	39	861	42
Former	3144	28	3537	37	3133	37	621	31
Current	4036	36	2709	28	2015	24	552	27
Previous MI								
Yes	3164	28	3445	36	3162	37	877	43
Previous HF								
Yes	578	5	962	10	1191	14	437	21
Previous CABG								
Yes	1088	10	1305	13	1194	14	185	9
Previous PCI								
Yes	1454	13	1251	13	956	11	162	8
ST depression								
Yes	5096	46	5475	57	5441	65	1403	69
Trial								
PRISM	1274	11	1005	10	781	9	172	8
PRISM-PLUS	693	6	603	6	495	6	124	6
PARAGON-A	737	7	728	8	631	8	183	9
PURSUIT	4082	37	3553	37	2763	33	550	27
PARAGON-B	1976	18	1513	16	1374	16	362	18
GUSTO IV	2393	21	2325	24	2424	29	658	32

CABG, coronary artery bypass graft; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Differences among age subgroups were highly significant ($p<0.001$).

Role of the funding source

The trials included in this analysis were sponsored by several pharmaceutical companies, which are mentioned in the main trial reports,[10–15] and in the acknowledgements. This study was designed, conducted and interpreted independently of the sponsors. They had the right to review the manuscript, but not to censor the findings. No separate industrial grant was obtained for this investigation.

RESULTS

Age subgroups and predictors

Overall, 11 155 (35%) patients were <60 years old, 9727 (31%) were aged between 60–69 years, 8468 (27%) were aged between 70–79 years, and 2049 (7%) were ⩾80 years old. Table 2 shows baseline characteristics for all age subgroups.

The proportion of women and of all patients with a history of diabetes, myocardial infarction or heart failure, and ST

Table 3 Treatment effect on various end points at 30 days according to age subgroups

	<60 years (n = 11 155)			60–69 years (n = 9727)			70–79 years (n = 8468)			⩾80 years (n = 2049)		
	Events	%	OR* (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)
Death†												
GP IIb/IIIa	70	1.1	0.86	165	2.9	0.98	281	5.6	0.91	115	9.5	0.90
Placebo/control	58	1.2	(0.61 to 1.23)	124	3	(0.77 to 1.24)	215	6.2	(0.75 to 1.09)	88	10.5	(0.67 to 1.21)
Nonfatal MI‡												
GP IIb/IIIa	372	5.7	0.83	428	7.6	0.85	437	8.8	1.02	112	9.3	0.91
Placebo/control	316	6.8	(0.72 to 0.97)	365	8.8	(0.74 to 0.99)	299	8.6	(0.87 to 1.19)	85	10.1	(0.68 to 1.23)
Death or MI												
GP IIb/IIIa	442	6.8	0.86	593	10.6	0.90	718	14.4	0.97	227	18.8	0.90
Placebo/control	374	8	(0.74 to 0.99)	489	11.9	(0.80 to 1.02)	514	14.8	(0.86 to 1.10)	173	20.5	(0.73 to 1.16)
CABG												
GP IIb/IIIa	828	12.7	1	931	16.6	0.92	860	17.2	0.99	102	8.5	1.07
Placebo/control	590	12.7	(0.90 to 1.13)	732	17.7	(0.83 to 1.03)	603	17.3	(0.88 to 1.11)	67	8	(0.77 to 1.47)
PCI												
GP IIb/IIIa	1839	28.3	0.92	1369	24.4	1.02	894	17.9	0.89	171	14.2	0.90
Placebo/control	1404	30.1	(0.84 to 0.99)	991	24	(0.93 to 1.12)	684	19.7	(0.80 to 1)	131	15.6	(0.70 to 1.15)
CABG or PCI												
GP IIb/IIIa	2618	40.3	0.93	2264	40.4	0.97	1721	34.5	0.93	268	22.2	0.93
Placebo/control	1960	42.1	(0.86 to 1.)	1699	40.8	(0.89 to 1.05)	1258	36.2	(0.85 to 1.02)	197	23.4	(0.76 to 1.15)
Major bleeding												
GP IIb/IIIa	90	1.5	1.90	118	2.3	1.94	174	3.8	1.58	63	5.7	2.46
Placebo/control	35	0.8	(1.28 to 2.81)	46	1.1	(1.38 to 2.74)	80	2.3	(1.21 to 2.07)	19	2.3	(1.46 to 4.14)

CABG, coronary-artery bypass graft; GP, platelet glycoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*OR of treatment effect between GP IIb/IIIa and placebo/control, GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers.
†Death within 30 days.
‡ Non-fatal myocardial infarction in patients who survived at least 30 days. Number of patients per age group <60 years: GP 6496, placebo/control 4659; 60–69 years: GP 5602, placebo/control 4125; 70–79 years: GP 4991, placebo/control 3477; >80 years: GP 1207, placebo/control 842.

Table 4 Treatment effects on death or myocardial infarction at 30 days according to age subgroups, by trial and overall

	PRISM	PRISM-PLUS	PARAGON-A	PURSUIT	PARAGON-B	GUSTO IV-ACS	Total*
	n = 3232	n = 1915	n = 2282	n = 10 948	n = 5225	n = 7800	n = 31 402
Age <60 yrs							
OR (95% CI)	1.13 (0.66 to 1.96)	0.98 (0.54 to 1.78)	1.65 (0.83 to 3.30)	0.72 (0.59 to 0.88)	0.90 (0.64 to 1.27)	1.01 (0.65 to 1.55)	0.86 (0.74 to 0.99)
Age 60–69 yrs							
OR (95% CI)	0.86 (0.53 to 1.38)	0.58 (0.35 to 0.96)	0.87 (0.55 to 1.39)	0.93 (0.77 to 1.20)	0.81 (0.59 to 1.12)	1.19 (0.85 to 1.67)	0.90 (0.80 to 1.02)
Age 70–79 yrs							
OR (95% CI)	0.63 (0.36 to 1.09)	1.02 (0.61 to 1.70)	0.83 (0.53 to 1.31)	0.91 (0.76 to 1.11)	1.11 (0.82 to 1.50)	1.15 (0.88 to 1.50)	0.97 (0.86 to 1.10)
Age ⩾80 yrs							
OR (95% CI)	0.45 (0.19 to 1.07)	0.94 (0.39 to 2.27)	0.82 (0.37 to 1.81)	1.27 (0.87 to 1.86)	0.84 (0.48 to 1.47)	0.80 (0.52 to 1.22)	0.90 (0.73 to 1.16)
All subgroups†	0.80 (0.60 to 1.06)	0.83 (0.62 to 1.11)	0.95 (0.72 to 1.25)	0.88 (0.79 to 0.98)	0.92 (0.78 to 1.10)	1.07 (0.90 to 1.27)	0.91 (0.86 to 0.99)
Age × GP IIb/IIIa interaction (p)‡	0.01	0.77	0.15	0.03	0.92	0.52	0.15

*ORs of each age subgroup adjusted for trial.
†Predictors included: age, sex, diabetes, smoking, previous myocardial infarction, previous heart failure, previous coronary-artery bypass graft , previous percutaneous transluminal coronary angioplasty, ST depression.
‡Adjusted for predictors: ORs adjusted for predictors and age trend. The interactions age × GP IIb/IIIa are significantly different among trials.

depression increased with age. Further, patients ⩾80 years had lower proportions of previous revascularisation procedures than younger patients. The proportion of patients >70 years old ranged between 30% in the PURSUIT and PRISM trials and 40% in the GUSTO IV-ACS trial.

End points at 30 days by age subgroups

The overall adjusted relative reduction in the odds of death or myocardial infarction at 30 days was 9% (OR 0.91; 95% CI 0.85 to 0.99). There was no difference in the relative benefit of platelet glycoprotein IIb/IIIa receptor blockers across age subgroups (p for interaction = 0.5), and this was also true for secondary efficacy end points (table 3). Interestingly, the ratio of non-fatal myocardial infarction over death decreased with increasing age. The overall adjusted relative increase in the odds of major bleeding was 83% (OR 1.83 (1.5 to 2.2)). This was especially high for patients aged ⩾80 years (OR 2.5 (1.5 to 4.1)), but there were no significant differences between ages (p for interaction = 0.3); (table 3).

Benefit of platelet glycoprotein IIb/IIIa receptor blockers per trial by age subgroups

With regard to the incidence of death or non-fatal myocardial infarction, two trials showed significantly different relative effects across age subgroups, but in opposite directions (table 4). The PRISM trial patients had a clear gradient of platelet glycoprotein IIb/IIIa receptor blocker effect relative to age: older patients had larger odds reductions than younger patients (p for interaction = 0.01). Conversely, younger PURSUIT trial patients had larger odds reductions than the older patients (p for interaction = 0.03). The interactions between platelet glycoprotein IIb/IIIa receptor blockers and age subgroup were heterogeneous across trials (p = 0.002).

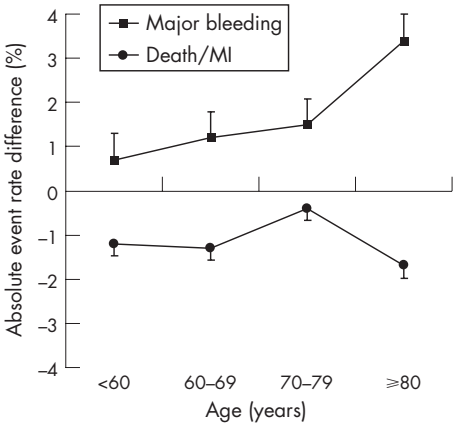

Figure 1 Absolute event rate differences between treatment arms (platelet glycoprotein IIb/IIIa vs placebo/control) by age subgroups in beneficial (death or myocardial infarction) and harmful (major bleeding) end points. Platelet glycoprotein IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers.

Benefit and harm of platelet glycoprotein IIb/IIIa receptor blocker across age subgroups

The absolute risk of death or myocardial infarction at 30 days correlated with age, varying from 8% in the youngest (<60 years) to 21% in the oldest group (⩾80 years). Major bleeding at 30 days also correlated with age, from 0.8% in the youngest to 2.3% in the oldest. For the overall relative reduction in the odds of death or myocardial infarction of 9%, the NNT was 105. For the overall relative increase in the odds of major bleeding of 83%, the NNH was 90.

The oldest patients had the largest absolute reductions of death or myocardial infarction, but also had larger absolute increases in major bleeding. Patients <70 years had higher NNTs and NNHs (149 and 163 for those <60 years, and 105 and 110 for those between 60 and 69 years) than those >70 years (87 and 55 for those between 70 and 79 years, and 67 and 56 for those >80 years). Figure 1 shows the absolute event rate difference between platelet glycoprotein IIb/IIIa receptor blocker and placebo/control arms for all age subgroups. We noted somewhat greater harm in patients ⩾70 years and a somewhat variable benefit across all age subgroups.

DISCUSSION

In patients with ACS without ST elevation, the relative reduction in the odds of death or myocardial infarction at 30 days with platelet glycoprotein IIb/IIIa receptor blockers was largely independent of age. The oldest patients had about threefold greater baseline risk than the youngest patients, not only for death or myocardial infarction but also for major bleeding. In the oldest patients, the use of platelet glycoprotein IIb/IIIa receptor blockers yielded larger absolute reductions in death/myocardial infarction, but also larger absolute increases in major bleeding rates compared with the youngest patients.

This meta-analysis had more statistical power than individual trials to explore how the platelet glycoprotein IIb/IIIa receptor blocker effects vary by age.[7–9 24] Individual trials did not report these effects in detail for similar age subgroups,[10 11 13–15]

and they analysed different end points. Previous analyses of the age effects in single trials have yielded inconclusive results.[25] Only the PURSUIT and GUSTO IV-ACS reported the same primary end point as we used in this paper. In addition, these analyses did not adjust for important predictors of the primary end point. We found that the PRISM and the PURSUIT trials showed significant differential relative effects of platelet glycoprotein IIb/IIIa receptor blockers across ages, but differences were in the opposite direction. We do not fully understand this phenomenon. We speculate that it could be related to the doses used and to the duration of the study drug infusion. This might have resulted in different levels of platelet inhibition in the PRISM trial (where the dose was later shown to produce suboptimal platelet inhibition in young patients compared with the PURSUIT trial (where the dose was not adjusted for older age or modest renal impairment), which might have had different consequences in younger and older patients.

The effects of other antithrombotics have been evaluated in elderly patients with unstable angina or NSTE–ACS.[9] The low molecular weight heparin enoxaparin, compared with unfractionated heparin, seemed to have greater relative and absolute benefit in patients aged ⩾65 years, compared with younger patients. When comparing clopidogrel plus aspirin with aspirin alone, there was a consistent 20% relative reduction in cardiovascular death, myocardial infarction or stroke in both elderly and younger patients. For platelet glycoprotein IIb/IIIa receptor blockers, we found an equivalent relative benefit across age subgroups, which translated into a greater absolute benefit in older patients compared with younger patients.

To describe the relative gain in primary efficacy end points by age subgroups, we defined a ratio of reduction of non-fatal myocardial infarctions with reduction of deaths. For instance, a ratio >1 shows a larger benefit in reduction of non-fatal myocardial infarctions compared with reduction of deaths. Given that the ratio of non-fatal myocardial infarction to death decreased with increasing age, the use of platelet glycoprotein IIb/IIIa receptor blockers in the oldest patients probably prevented more deaths than non-fatal myocardial infarctions.

Most trials, meta-analyses and systematic reviews have neglected the contribution of major bleeding rates in the evaluation of the net platelet glycoprotein IIb/IIIa receptor blocker effectiveness across age subgroups in patients with NSTE–ACS.[1–4 10–15 26–31] Elderly patients have a higher absolute risk of major bleeding.[6 32] Therefore, the interpretation of the overall platelet glycoprotein IIb/IIIa receptor blocker efficacy needs to incorporate this harm. Although there was a trend towards increasing bleeding risk with increasing age, this was nowhere close to being statistically significant, and it should be interpreted cautiously given the small number of patients in the highest age category.

An appropriate dosing of platelet glycoprotein IIb/IIIa receptor blockers is a requisite to obtain greater benefit and less harm in elderly patients with NSTE–ACS. The CRUSADE registry showed that platelet glycoprotein IIb/IIIa receptor blockers were underutilised and misdosed in elderly patients, who are at higher risk for adverse cardiac events.[33] An essential factor that increases the risk of major bleeding in elderly patients is poor renal function, which is associated with higher serum levels of platelet glycoprotein IIb/IIIa receptor blockers. Doses used in early trials were more aggressive than currently recommended doses, which are adjusted for renal dysfunction. Thus, elderly patients with NSTE–ACS should receive adequate doses of platelet glycoprotein IIb/IIIa receptor blockers to obtain the expected clinical benefit, and these doses should be adjusted for their level of renal function to avoid major bleeding events.

A recent decision analysis evaluated the efficacy of an unspecified potential drug on survival in patients with myocardial infarction and unstable angina,[5] and included serious adverse events (fatal complications) as an element of the evaluation of benefit–risk balance by age-related baseline risks. The authors used a registry database, and a definite primary end point (mortality at 1 year). The estimate of effectiveness was larger than in our randomised data (relative risk reduction 25%, absolute risk reduction 2%), and the registry population was more heterogeneous in risk (baseline risk of 2.3% in the youngest vs 27% in the oldest). The authors defined a threshold beyond which the treatment benefit would be outclassed by the treatment harm, and found that the fatal complication rate would have to be sevenfold greater in the oldest compared with the youngest age group to outweigh the survival benefits associated with treatment. These results need to be interpreted cautiously, given that most major events in these patients do not lead to death. Moreover, retrospective observational data may sometimes inflate estimates of treatment efficacy.[34]

Some limitations of this study should be acknowledged. Firstly, even with over 30 000 randomised patients, subtle age interactions could have been missed, especially for rare events such as death. We did not see any age interactions for death based on the available data (not reported), and the clinical significance of subtle interactions is debatable. Secondly, the total number of patients in the ⩾80 age subgroup (n = 2049) was small, and <25% of each of the other three groups (n>8400). Thirdly, a substantial number of missing values for a few important predictors (blood pressure, heart rate, CK-MB) limited some possibilities of adjusted analysis. However, the results with imputed data yielded similar conclusions (not shown). Fourthly, additional research into the appropriate weighting of events is needed to allow a more direct comparison between benefits and harms.

Some nuances should be considered in interpreting these results. The trials included broad populations of patients with ACS. Through analysis of subgroups, it seems evident that higher risk patients, such as those with positive troponins, diabetes, and perhaps ST segment depression, achieve the greatest benefit. Furthermore, it is likely that patients treated with the aggressive revascularisation strategy achieve more benefit than those treated with the conservative strategy. The trials themselves were heterogeneous, as the GUSTO IV-ACS showed no benefit and perhaps a detrimental effect of abciximab, and PURSUIT used a very liberal definition of myocardial infarction that minimised the differences between eptifibatide and placebo. Finally, the category of major bleeding overestimates risk relative to the risk of blood transfusion, which is a more direct measure of risk and occurs less frequently. The EARLY ACS trial enrolls patients without age limit, tests whether the benefit of antithrombotic drugs is similar between elderly and young patients, and is also addressing each of the above issues.[35] Allowing for these caveats, our analysis provides estimates for NNTs and NNHs by age subgroups that may be used in clinical decision making for the use of platelet glycoprotein IIb/IIIa receptor blockers in patients with NSTE-ACS.

In conclusion, the relative risk reduction of death or myocardial infarction with platelet glycoprotein IIb/IIIa receptor blocker is independent of age in patients with non-ST-elevation ACS. Larger absolute reductions of death or myocardial infarction, were observed in the oldest compared with the youngest patients, as well as larger absolute increases in major bleeding rates. Attention should be given to optimising the benefit to elderly patients without increasing bleeding, by

ensuring that doses adjusted for renal function are given, and elderly patients should be monitored more intensively.

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